

Application Serial Number 09/991,445

Attorney Docket No. 48175-00005

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CENTRAL FAX CENTER****DEC 15 2006****REMARKS**

Claims 1-10 and 12-20 are currently pending and Claims 1-10 and 12-20 have been rejected by the Examiner. Applicants submits that Claims 1, 10 and 17 have been amended. Support for the amendment is found in the specification at page 17, paragraph 52, where it is stated that: "Surfactants for use in the present invention . . . aids in the formation and maintenance of the bubble membrane by forming a layer at the interface between the phases." Further at page 24, paragraph 0080 where "lipid coated, non-liposomal microbubbles" are disclosed in the formation of the microbubbles.

The presently amended claims are drawn to *inter alia* a microbubble for the in vivo transport of physiological gases wherein the microbubble comprises a membrane entrapping at least one fluorocarbon gas and at least one modifier gas, wherein the membrane is a monolayer of surfactant, wherein the ratio of the modifier gas to the fluorocarbon gas is from about 1:100 to about 1000:1, wherein the partial pressure of the resulting gas mixture at 37°C is greater than the equilibrium partial pressure of the fluorocarbon gas, and wherein the microbubble grows and shrinks to maintain osmotic equilibrium with the physiological gas saturation of the surrounding external medium.

Rejection under obviousness double patenting

Claims 1-10, and 12-20 have been rejected under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patents 6,372,195; 6,258,339; 5,695,741; 5,639,443; 5,798,091; 5,804,162 and 6,193,952. Applicants wish to thank the Examiner for holding this rejection in abeyance until an allowable subject matter has been declared.

Application Serial Number 09/991,445

Attorney Docket No. 48175-00005

Rejection under 35 U.S.C. §103(a)

Claims 1-10, 13-18, and 20 have been rejected under 35 U.S.C. §103(a) over U.S. Patent 5,413,774 ("Schneider"). Applicants respectfully traverse.

The Examiner maintains that "Schneider" meets the limitations of the present invention including the membrane of the present invention. Examiner states that the Schneider's microbubbles comprise a membrane comprising phospholipids or albumin (see "Schneider" U.S. Patent 5,413,774 at col. 13-14).

Examiner further asserts that "Schneider" only fails to "specifically recite the instantly claimed ranges of modifier gas to fluorocarbon gas" and a skilled artisan will "optimize the concentrations of individual gases" in "Schneider" microbubbles by "routine experimentation to observe the most effective clinical results."

Applicants respectfully disagree. Applicants note that presently amended Claims 1, 9 and 13 include a membrane comprising a monolayer of surfactant in contrast to lamellar form of surfactants of "Schneider." See "Schneider" U.S. Patent 5,413,774 at col. 4, lines 36-42 and col. 10, lines 55-56.

First, Applicants note that "Schneider" liposomes have hydrophilic interiors, created by laminar phospholipids (see, e.g., col. 5, ll. 23-25), so that water is comfortable when present inside these liposomes. "Schneider" discloses gas filled liposomes containing microbubbles bounded by an "evanescent gas liquid interfacial closed surface." See "Schneider" U.S. Patent 5,413,774 col. 14, lines 35-36. By contrast, Applicants' microbubble is bounded by a membrane with a monolayer of surfactant, which implicitly comprises a hydrophobic (water-hating) interior. A *hydrophobic* interior is more aptly suited for the use of a fluorocarbon osmotic stabilizer gas which in turn dramatically increases the stability of the gas dispersions of the

Application Serial Number 09/991,445

Attorney Docket No. 48175-00005

present invention. Furthermore the hydrophobic interior of the surfactant layer contains the fluorocarbon within the bubble and the surfactant membrane with a layer of surfactant allows diffusion of the modifier gas. "Schneider" discloses that less water soluble and higher molecular weight gases are best suited as replacement gases. See "Schneider" U.S. Patent 5,413,774 col. 11, lines 30-34. Thus "Schneider" relies on the gas-water interaction within the liposomes. In sharp contrast the interaction of the fluorocarbon gas and the membrane surfactant layer in Applicants' invention maintains an osmotically stabilized microbubble. "Schneider" does not disclose a modifier gas such as oxygen which diffuses through the bubble membrane with a layer of surfactant.

Second, "Schneider" discloses replacing or substantially replacing a first gas with a second gas in his microvesicles. Additionally, "Schneider" merely mentions that the step of replacement of the initial gas by the replacement (the fluorocarbon) gas in the microbubbles "can be repeated one or more times to ensure complete replacement of the original gas by the new one." (See "Schneider" U.S. Patent 5,413,774 col. 5, lns 16-18). Thus, the final microbubbles of "Schneider" contain one gas, the fluorocarbon.

"Schneider" does not suggest or disclose a membrane entrapping at least one fluorocarbon gas and at least one modifier gas, wherein the membrane is a monolayer of surfactant. The Examiner states that "products of identical chemical composition cannot have mutual exclusive properties" and "if the prior art teaches the identical chemical structure the disclosed properties are necessarily present." "Schneider" does not disclose or teach the present microbubbles; therefore, the gas transport properties of the instant invention vary considerably from those of "Schneider."

Application Serial Number 09/991,445

Attorney Docket No. 48175-00005

Examiner maintains that it is obvious to optimize the ratio of gases when *general* conditions are disclosed. As noted above "Schneider" does not disclose conditions present in the Applicants' microbubbles. "Schneider" was specifically concerned about water-gas interaction in contrast to surfactant-gas interactions of the present invention. Accordingly, Applicants fail to understand how to optimize the concentrations of individual gases by routine experimentation as suggested by the Examiner when "Schneider" discloses *specific* water-gas interactions.

For the reasons given above, Applicants respectfully request the withdrawal of this ground of rejection.

Rejection under 35 U.S.C. §103(a)

Claims 12,19 have been rejected under 35 U.S.C. §103(a) over "Schneider" in view of U.S. Patent 4,265,251 ("Tickner"). Applicants respectfully traverse.

"Schneider" does not describe nor disclose the limitations of the present invention as noted above.

Examiner acknowledges that "Schneider" does not teach oxygen. Applicants note that "Schneider" merely states that air in the microbubble is replaced by a physiologically acceptable gas and sets forth criteria based on water solubility as the replacement gas. According to "Schneider," less water-soluble gases with higher molecular weights are best suited as replacement gases; thus, "Schneider" arrives at the fluorocarbons for replacement of air inside the microvesicles.

The Examiner also asserts that "Tickner" discloses use of oxygen in the contrast agents and maintains that gases such as oxygen, nitrogen, and Freons are substantially interchangeable and are functional equivalents. Thus, according to "Tickner," a microbubble having only oxygen or nitrogen is functionally equivalent to a microbubble having a fluorocarbon. This conclusion is

Application Serial Number 09/991,445

Attorney Docket No. 48175-00005

explicitly rejected by "Schneider," which states that microbubbles filled with "common gases such as air, methane or CO₂" will collapse (col. 3, ll. 32-35), and prior art gases such as "air, nitrogen, CO₂ and the like" should not be used (see col. 5, ll. 53-56).

Thus, Applicants fail to appreciate how gases such as oxygen, nitrogen and Freon are substantially interchangeable and functional equivalents as asserted by the Examiner. By contrast the presently amended claims disclose perfluorocarbons and fluorocarbons as gas osmotic agents with partial pressure of the resulting gas mixture at 37°C greater than the equilibrium partial pressure of the osmotic agent and a modifier gas such as oxygen which diffuses through the bubble membrane with a layer of surfactant.

Thus, Applicants contend that "Tickner" does not cure the deficiency of "Schneider" and provides no motivation to combine. Accordingly, Applicants respectfully request the withdrawal of this ground for rejection.

Rejection under 35 U.S.C. §103(a)

Claims 1-10, 12-20 have been rejected under 35 U.S.C. §103(a) over "Schneider" in view of U.S. Patent 5,536,753 ("Clark"). Applicants respectfully traverse.

Examiner acknowledges that "Schneider" does not teach oxygen, and for reasons discussed above, Applicants note that "Schneider" does not describe nor disclose the present invention.

Examiner maintains that the liquid emulsions disclosed by "Clark" are not very different from the gas microbubbles of the present invention because "Clark" discloses that perfluorocarbon-containing emulsions are *safe* oxygen transport agents.

Applicants respectfully submit that the liquid emulsions discussed in "Clark" could not be used in combination with "Schneider" to obtain the microbubbles of the present invention.

Application Serial Number 09/991,445

Attorney Docket No. 48175-00005

"Clark" discloses that fluorocarbons such as perfluoroindane or perfluorocyclohexane, which both have high vapor pressures, cause gas embolism in subjects resulting in *death*. See "Clark" at column 1, lines 50 to 52 (discussing the danger of a high vapor pressure of 32.8 mm Hg). Therefore "Clark" teaches away from osmotic agents of the present invention with high vapor pressures (about 75 mm Hg or above), which are required for osmotic stabilization within the microbubbles of the present invention.

Applicants note that the modifier gas (e.g. air) diffuses through the surfactant layer bubble membrane to maintain osmotic equilibrium in contrast to "Clark." "Clark" merely mentions that oxygen is transported in a liquid perfluorocarbon emulsion and is silent on how the fluorocarbon vapor is contained within the emulsion. By contrast, in Applicants' microbubble the fluorocarbon vapor is contained within the bubble by the surfactant membrane and provides for safe transport of the modifier gas. Furthermore, Clark's emulsions require hydrophobic oils, whereas Applicants' microbubbles do not. See for example, "Clark" at Claim 1. This is not an insubstantial difference. Applicants submit that hydrophobic oils would negatively impact the osmotic stabilization process and would interact with the surfactant layer membrane.

Applicants submit that the prolonged controlled-release circulation time of Applicants presently amended microbubble compositions is in direct contrast to the rapid release rates of the gases from the preferred emulsions disclosed in "Clark". Id. Simply put, the compositions of "Clark" have a substantially shorter half-life than the compositions of Applicants' invention.

Thus Applicants contend that "Clark" does not cure the deficiency of "Schneider" and provides no motivation to combine. Accordingly, Applicants respectfully request the withdrawal of this grounds for rejection.

Application Serial Number 09/991,445

Attorney Docket No. 48175-00005

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DEC 15 2006


Applicants submit that all the claims are in condition for allowance and Applicants respectfully request that all claims be allowed.

Applicants request that any questions concerning this matter be directed to the undersigned at (609) 844-3023. If a telephone conference would be of assistance in advancing the prosecution of the present application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided.

Applicants also authorizes the charge of any deficiency and/or the credit of any overpayment to deposit account 50-1943.

Respectfully submitted,

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